UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,462	05/05/2006	Makrina Savvidou	HO-P03236US0	8934

29053 7590 09/22/2009

FULBRIGHT & JAWORSKI L.L.P
2200 ROSS AVENUE
SUITE 2800
DALLAS, TX 75201-2784

EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	PAPER NUMBER
1632	
MAIL DATE	DELIVERY MODE
09/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,462	SAVVIDOU ET AL.	
	Examiner	Art Unit	
	ANOOP SINGH	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 May 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-8 and 11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 6-8, 11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendment to the claims filed May 21, 2009 have been received and entered. Claim 1 has been amended, while claims 2-5, 9-10, 12-28 have been canceled. Claims 1, 4- 11 are pending.

Election/Restrictions

Applicant's election without traverse of claims 1-2 and 4-11 in the reply filed on August 31, 2007 was acknowledged.

Claims 1, 6-8 and 11 are under consideration.

Maintained -Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6-8 and 11 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining that a pregnant woman is at risk of developing pre-eclampsia or whether that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises: (a) measuring plasma concentration of asymmetric dimethylarginine (ADMA) in a pregnant woman at risk of developing pre-eclampsia or her fetus being at risk of developing IUGR at a stage of pregnancy from 23 to 25 weeks gestation; and (b) plasma ADMA level in said women greater than 1.5 microM/L indicates that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR, does not reasonably provide enablement for determining that a pregnant woman is at risk of developing pre-eclampsia by measuring ADMA at any other stage of pregnancy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Applicants' arguments filed May 21, 2009 have been fully considered and are persuasive in parts. Applicants' cancellation of claims 4-5, 9 and 10 renders their rejections moot. Applicants' amendment of base claim 1 to recites measuring the level of ADMA in the plasma level, only in part obviates the grounds for rejection.

Applicants argue that measuring ADMA in a plasma sample taken from pregnant woman at stage of pregnancy from 4 to 25 weeks gestation would not require undue experimentation. Applicants assert that one of skilled in the art could measure ADMA levels and compare to the threshold level. Applicants assert that the specification provides sufficient guidance to allow one of ordinary skill in the art to make and use the present invention without undue experimentation.

Such is not found persuasive, because instant analysis is based on the predictability of the risk of developing pre-eclampsia (PE) or IUGR is based on the presence of plasma ADMA level greater then 1.5 μmol/L at any stage of pregnancy. As stated before that applicants agree that pre-eclampsia is a multi factorial disease, which involves changes in, amongst others, a cardiovascular function, metabolic function and renal function (see Cooke et al Circulation. 2004 Apr 20;109(15):1813-8, Fard et al, Arterioscler Thromb Vasc Biol 2000; 20: 2039-2044 and Kielstein et al Am J Kidney Dis. 2005; 46: 186–202, Fang et al Hypertension 2006; 48: 724-729, all of the record). Thus, it is apparent that level of ADMA is influenced by different conditions and disorders and may not be specific risk marker for PE or IUGR in the first trimester. The guidance provided in the specification shows ADMA level greater than1.5 microM/L at 23 to 25 weeks of gestation indicates risk of developing pre-eclampsia or risk of developing IUGR in pregnant women.

It should be noted that instant claims embrace a method of determining that a pregnant woman is at risk of developing pre-eclampsia or that her fetus is at risk of developing IUGR by (i) measuring asymmetric dimethylarginine (ADMA) levels in "a" pregnant woman of varying gestational age (4-25 week of gestation) and (ii) determining that the women is at risk of developing PE or IUGR of the level of ADMA in the plasma is greater than 1.5 micro mol/L. With respect to applicants' argument that one could measure ADMA levels and compare to the threshold level, it is noted that as recited method of claim 1 step 1 recite measuring ADMA in any pregnant woman and does not require comparing to any control to arrive at any threshold

number as argued by the applicants. Further, the specification fails to disclose a threshold level of ADMA as a preclampsia risk indicator in pregnancy in first trimester. The specification teaches women with bilateral notches had significantly higher levels of ADMA compared to the women with normal uterine artery Doppler waveforms (2.4 μmol/L vs. 0.81 μmol/L respectively, Figure 2, page 21) which is at least three time of normal pregnancy level. With respect to applicants' argument that the data demonstrates that a plasma ADMA level measurement of greater than 1.5 micro mol/L can be used determine that a woman is at risk of developing IUGR or pre-eclampsia, it is noted that the specification discloses that women who subsequently developed pre-eclampsia had significantly higher levels (2.21-3.21μmol/L) of ADMA (Table 3), however, specification also teaches that women in absence of notches with raised concentrations of ADMA did not develop pre-eclampsia (see table 3). It is noted that only women with notches and a high ADMA developed pre-eclampsia. In the instant case, there is no evidence on record that establishes nexus between higher ADMA level in plasma of a pregnant woman at a first trimester stage of pregnancy from 4 to 15 weeks gestation. In fact, Ellis et al (Acta Obstet Gynecol Scand. 2001 Jul;80(7):602-8, IDS) report no convincing correlations between ADMA and clinical parameters (see page 606, col. 1, para. 1). In view of these comments, ADMA plasma levels cannot be used to determine risk of preclampsia in first trimester pregnancies. Furthermore, Contrary to the limitation of claim 7, Ellis et al teach that the ADMA/SDMA quotient is significantly lower in subjects with severe preeclampsia than in controls, reflecting a marked elevation of SDMA. These results are also contrary to the teaching of Pettersson et al (Acta Obstet Gynecol Scand 1998; 77: 808–813). The unpredictability of establishing nexus between first trimester uterine artery resistance and maternal serum concentration of ADMA is further evidenced by a recent report that states "[n]o significant difference was found in maternal serum ADMA between pregnancies with first trimester high resistance uterine artery blood flow and control" (abstract) (Prefumo et al Ultrasound Obstet Gynecol, 2008, 31, 153-157) (emphasis added). It is emphasized that several years after filing of this report Prefumo concludes that a long longitudinal study would be required to examine whether concentration of maternal ADMA in the first trimester co relates with the onset of the pre-eclampsia (se page 156, col. 1, last para.) MPEP 2164.05(a) also states "If individuals of skill in the art state that a particular invention is

not possible years after the filing date, that would be evidence that the disclosed invention was not possible at the time of filing and should be considered. In *In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513-14 (Fed. Cir. 1993)*. Therefore, it is evident from the teaching of the cited references filed before, and after filing of this application show measuring ADMA level at different stage of pregnancy, without any comparison step of threshold value in base claims would not be reliable risk marker for PE or IUGR. It should be firther noted that the unpredictability of a particular art area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See *Ex parte Singh*, 17 USPQ2d 1714 (BPAI 1991). It is also well established in case law that the specification must teach those of skill in the art how to make and how to use the invention as broadly claimed. In re Goodman, 29 USPQ2d at 2013 (Fed. Cir. 1994), citing *In re Vaeck*, 20 USPQ2d at 1445 (Fed. Cir. 1991). Given the lack of guidance provided by the specification it would have required undue experimentation for one of skill in the art to make and use the invention as claimed without a reasonable expectation of success. It is apparent that underlying condition and gestation age could greatly effect the level of plasma ADMA level. Given such differences in the level of ADMA at varying gestation age of a preganat woman as embraced by the claims, particularly when taken with the lack of guidance provided by the specification, it would require undue experimenattaion to make and use the inevntion without resonable expectation of sucess.

It is emphasized that the claims are directed to measuring ADMA levels in plasma of a pregnant women that is limited by determining that women is at risk of developing IUGR or PE if the level of ADMA is greater than 1.5 micro mol/L. Examiner had previously indicated that the state of the art generally recognized that the reference used for comparison with the test level of the AMDA level may vary, depending on aspect of the invention being practiced. These values are subjective to sample population, other variables (age, gender, hormonal status, ethnicity, disease state), assay system and are subjective to different interpretation by different artisans (see López -Jaramillo (J Hypertens. 2005; 23(6): 1121-9 and references therein, art of record). Given that levels of ADMA may vary depending on values that are subjective to sample population such as age, gender, hormonal status, ethnicity, disease state, it is thus unpredictable as to how one might use any reference marker profile comprising ADMA identified in a plasma in the analysis of a biomarker profile obtained from any other pregnant women with underlying

disease that influence ADMA level (kidney disease, hypertension). The specification fails to provide an enabling disclosure for the claimed invention because the specification fails to provide sufficient guidance as to how an artisan of skill would have practiced the claimed method in any pregnant women of any ethnicity suffering from multiple chronic disorders to predict the risk of developing PE or risk of fetus developing IUGR if ADMA level is greater then 1.5 micro mol/L (see the discussion before). An artisan would have to carry out extensive experimentation to make and use the invention, and such experimentation would have been undue because art of predicting that a pregnant women is at risk of developing PE by measuring the level of ADMA in any tissue or fluid without reasonable expectation of success.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1 and 7 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Boger (WO 2002/14873, 2/21/2002, IDS), Holden et al (Am J Obstet Gynecol. 1998; 178(3):551-6, art of record).

Claims are directed to method of determining that a pregnant woman is at risk of developing pre-eclampsia (PE) or that her fetus is at risk of developing intrauterine growth restriction (IUGR), which method comprises: (a) measuring asymmetric dimethylarginine (ADMA) in a pregnant woman at a stage of pregnancy from 4 to 25 weeks gestation; and (b) determining that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA is greater than 1.5 micromol/L in the woman. Instant rejection is applied to the extent claim reads on measuring if the ADMA level is greater than 1.17 micromol/L in the pregnant woman to suggest subject is at risk of developing PEWith respect to claim 1, Boger et al teach a method of detecting the risk of developing a disease including pre-eclampsia that is associated with NO metabolism by (a) measuring the level of

ADMA and SDMA (see claims 1 and 9). Boger et al also disclose that preeclampsia is a disease of the NO metabolism leads to constriction of arteries which induces high blood pressure in the mother and poses a risk to the unborn child due to reduced placental perfusion (see page 2) With respect to claim 7 and 8, Boger et al contemplate measuring the ration of ADMA to SDMA in the plasma of the patient (see claim 14, 20 and 21). It is also disclosed that subject suffering from chronic condition (CHF, example 4) show ADMA concentration of 4.1 μM/L as compared to 1.0 μM/L in normal subject. Boger teach a method of measuring ADMA in a subject to determine the risk of developing chronic condition if ADMA level is high and also contemplated to determine ADMA level in other conditions that increase high blood pressure such as PE, but Boger differed from claimed invention by not disclosing measuring ADMA level in pregnant women at a stage of pregnancy from 4 to 25 weeks gestation.

The deficiency of Boger is cured by Holden who teaches measuring plasma ADMA level in 145 pregnant women that included pregnancy of all stages (including second trimester). It is noted that Holden et al also determined the level of ADMA which is at least 0.52 μmol/L to 1.17 μmol/L depending upon stage of pregnancy. This would meet the breadth of the claim measuring pregnancy at different stage of pregnancy (4-25 weeks) that is embraced by the teaching of Holden (see page 553, Figure 1 B). It is noted that Holden et al conclude that during later stage of pregnancy circulating concentrations increase and, when pregnancy is complicated by preeclampsia. It should be noted that Holden et al teach that mean plasma ADMA level in PE subject was 1.17±0.42 (1.59-0.75μM/L) as compared to control subject. The range taught by Holden encompasses 1.5 uM/L as claimed. Thus, method of Holden is primarily directed to study the role for ADMA in the changes in blood pressure seen in preeclampsia pregnancy (see abstract and page 555, col. 1, para. 4).

It would have been obvious for one of ordinary skill in the art at the time of invention to modify the method of Boger by measuring the ADMA level in the pregnant women at varying stage of pregnancy from 4-25 weeks gestation using the known method disclosed by Holden. It would have been prima facie obvious to one of ordinary skill in the art to combine the known methods of Boger and Holden to measure the ADMA level in a pregnant women at a stage of pregnancy from 4-25 and determine the level of ADMA to predict the risk of developing

preeclampsia particularly since both generally embraced the potential of measuring ADMA level to determine the risk of developing pre-eclampsia. One who would have practiced the invention would have had reasonable expectation of success since Boger and Holden both taught method to measure ADMA level in the plasma of subject to determine if the subject is at risk of developing PE, while combining the teaching Boger and Holden would have resulted in a determining the level of ADMA that is greater then 1.17 μM/L to establish risk of developing pre-eclampsia.

Therefore, the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention.

"The art rejection may be overcome if applicant amended the base claim to include additional method step of carrying Doppler flow form analysis of the uterine arteries to determine pregnant woman with bilateral notches and than measuring asymmetric dimethylarginine (ADMA) in a pregnant woman at a stage of pregnancy from 23 to 25 weeks gestation; and (b)-determining that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA is at least 3 times greater than the ADMA level in the normal pregnancy ."

Response to arguments

Applicants' arguments filed May 21, 2009 have been fully considered but are not persuasive. Applicants' cancellation of claims 4-5 and 9 renders their rejections moot. Applicants argue that Boger and Holden fail to disclose or suggest determining that a woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA in a plasma sample is greater than 1.5 μM/L, as required by claim 1.

Such is not persuasive; because Holden et al teach that a level of ADMA in a pregnant woman of 1.17±0.42 (1.59-0.75μM/L) is sufficient to indicate that woman is at risk of developing pre-eclampsia. In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicants have further engaged in selective reading of the teachings of Boger and Holden to

formulate the grounds for not teaching the invention. It should be noted that the ultimate goal of measuring plasma ADMA in patient is to determine if the patient is at risk of developing PE. As previously indicated, contrary to applicants' assertion prior art of Holden recognized that higher ADMA level (greater than 1.17±0.42 or a range 1.59-0.75 μM/L) in the plasma of a pregnant woman is indicative of PE. Further, it is noted that claimed method recite two method steps (1) measuring ADMA in a plasma sample taken from any pregnant woman at a stage of pregnancy from 4 to 25 weeks gestation, and determining that the woman is at risk of developing pre-eclampsia or her fetus is at risk of developing IUGR if the level of ADMA in the plasma sample is greater than 1.5 μM/L. In the instant case, it would have been *prima facie* obvious to one of ordinary skill in the art to combine the known methods of Boger and Holden to measure the ADMA level in a pregnant women at any stage of pregnancy from 4-25 and determine the level of ADMA of more than 1.17±0.42 μM/L to predict the risk of developing preeclampsia particularly since both generally embraced the potential of measuring ADMA level to determine the risk of developing pre-eclampsia. One of ordinary skill in the art after studying Holden would recognize that ADMA level of greater than 1.17±0.42 μM/L in the plasma of a pregnant woman is sufficient to predict that the subject is at risk of developing pre-eclampsia. Thus, the rejection of claims 1 and 7 is maintained for reasons of record and the foregoing commentary.

Conclusion

No claims allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANOOP SINGH whose telephone number is (571)272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Deborah Crouch/
Primary Examiner, Art Unit 1632

Anoop Singh
AU 1632